Remarks/Arguments

1. Amendments

Claims 25 and 31-44 are pending in the application. Applicants have amended claim 25 to recite that the antibody inhibits TGFα-HII. Support for this amendment can be found in the specification at page 24, para [119] line 3 which states that the antibodies bind to and inactivate TGFα-HII.

Applicants expressly reserve the right to pursue any canceled matter in subsequent continuation, divisional or continuation-in-part applications.

The specification was amended at page 1 to update the status of the priority applications.

2. Objection to the Amendment to the Specification at page 5, line 3.

The amendment to page 5, line 3, paragraph [0027] filed 6/12/06 stands objected to under 35 U.S.C. 132(a) because it allegedly introduces new matter into the disclosure.

Applicants amended the paragraph as follows:

The full-length polypeptide of the present invention as set forth in SEQ ID NO:2 has a putative signal sequence which comprises amino acid 1 through amino acid 45 of SEQ ID NO:2 which aids in secretion of the polypeptide from the cell. The polypeptide is further processed wherein amino acid 46 through amino acid ~~214~~ 259 of SEQ ID NO: 2 are cleaved from the polypeptide since this stretch of amino acids is a putative precursor sequence. Further, amino acid ~~264~~ 310 through amino acid 344 represent a putative transmembrane portion which is thought to be necessary to direct the polypeptide to particular target locations for the carrying out of biological functions as herein after described. The transmembrane portion may also be cleaved from the polypeptide such that the putative soluble portion of the polypeptide of the present invention comprises amino acid ~~215~~ 260 through amino acid ~~264~~ 309 of SEQ ID NO:2

In particular, the specification was amended at page 5, line 3, paragraph [0027] to correct obvious typographical errors regarding the numbering of the functional regions within the amino acid sequence of SEQ ID NO:2 as mentioned on page 5 of the specification.

This correction is necessitated by the filing of the amended Sequence Listing SEQ ID NO:2 which renumbered the amino acid sequence to begin with amino acid number +1. SEQ ID NO:2 originally filed with the PCT application had the amino acid sequence beginning with number –45.

We submit that the correct numbering of the functional regions of SEQ ID NO:2 (i.e. according to the numbering with position 1 assigned to the N-terminal methionine residue) are:
putative signal sequence – amino acids 1 to 45 of SEQ ID NO:2;
putative precursor sequence – amino acids 46 to 259 of SEQ ID NO:2;
putative soluble portion – amino acids 260 to 309 of SEQ ID NO:2; and
putative transmembrane portion: - amino acids 310 to 344 of SEQ ID NO:2.

It should be acknowledged that there are some inconsistencies in the specification as filed and in the numbering of the original SEQ ID NO:2 filed with the PCT application and the current SEQ ID NO:2. This is apparent from the numbering of the signal sequence to positions 1 to 45 at page 5 of the PCT specification, but the numbering of signal sequence in the original SEQ ID NO:2 filed with the PCT starting with position –45.

It is understood by one skilled in the art that signal sequences are generally present in the N-terminus of a secreted or membrane bound protein. Thus it would be immediately evident to a skilled person that the allocation of positions 1 to 45 refers to an amino acid sequence the numbering of which starts with Met at +1 and not at –45. It would therefore have been obvious that there is a typographical error in the original PCT specification.

Further items that would lead a skilled person to conclude that the annotations on page 5 of the description as filed are incorrect, for example, the transmembrane portion is ascribed to amino acid positions 264 to 344. However, the numbering of SEQ ID NO:2 as originally filed with the PCT application ends at position 329. Therefore it would have been obvious that there is a typographical error in the PCT specification.

Thus one skilled in the art would look to the specification to arrive at the correct functional regions. As discussed above, using SEQ ID NO:2 commencing with methionine as

amino acid +1, one skilled in the art would recognize that the signal sequence region was from amino acids 1 to 45. One skilled in the art would also recognize that the entire amino acid sequence would be amino acids 1 to 374. One skilled in the art would look at the remainder of the specification and add +45 to certain amino acid regions given on page 5 to make the regions consistent with the teaching in the rest of the specification.

Concerning the putative soluble region (amino acids 260 to 309 of SEQ ID NO:2) a skilled person would look to Example 2. Specifically on page 240, paragraph [0146] it is described that by use of the primers having the nucleotide sequences depicted under SEQ ID NO:9 and 10, a construct encoding the putative soluble portion can be amplified. This construct is indicated to range from nucleotide 1100 to 1248 of SEQ ID NO:1. A comparison of this nucleotide sequence with that shown in now filed SEQ ID NO:1 (this sequence is numbered beginning with +1, according to corrected SEQ ID NO:2) reveals that this nucleotide sequence exactly encodes amino acids 260 to 309 of the amino acid sequence given in Figure 1. Applicants note that position 309 in SEQ ID NO:2 (methionine as position +1) corresponds to amino acid 264 in the original SEQ ID NO:2.

The Examiner states that nucleotide 1248 of SEQ ID NO:1 is found in the noncoding nucleotides. However, a careful analysis of SEQ ID NO:1 indicates that nucleotide 1248 is found within the coding region at amino acid residue 309.

The Examiner states that the application makes no mention of primers with respect to Figure 1. Applicant agrees that the specification refers to SEQ ID NO:1 which was always numbered from nucleotide +1.

Concerning the putative precursor region, (amino acids 46 to 259 of SEQ ID NO:2), a person skilled in the art given the understanding of the soluble region would understand from the paragraph at page 5 that the precursor region is followed by the soluble region. Thus a person skilled in the art would derive that the precursor region ranged from position 46 to position 259 of SEQ ID NO:2.

Concerning the putative transmembrane region (amino acids 310 to 344 of SEQ ID NO:2) the C-terminus of this region is correctly stated on page 5. A skilled reader would not doubt this because this position does not conflict with the other sequence ranges and the renumbering of SEQ ID NO:2 gives the value 344 a reasonable meaning. Regarding the N-terminus of this

region, a skilled reader would understand from page 5 that the transmembrane region follows the soluble region and thus the N-terminus would be amino acid 310.

From the forgoing it is clear that the requested re-numbering of the annotations for the functional regions of SEQ ID NO:2 in the specification find a basis in the application as filed. Entry of the amendment to the specification is respectfully requested.

3. Rejection under 35 U.S.C. § 112, first paragraph, written description

Claims 25 and 31-44 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification.

The Legal Test for Written Description

The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is "whether the disclosure of the application as originally filed reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter, rather than the presence or absence of literal support in the specification for the claim language."[1] [2];. The adequacy of written description support is a factual issue and is to be determined on a case-by-case basis.[3] The factual determination in a written description analysis depends on the nature of the invention and the amount of knowledge imparted to those skilled in the art by the disclosure. [4] [5]

In *Environmental Designs, Ltd. v. Union Oil Co.*,[6] , the Federal Circuit held, "Factors that may be considered in determining level of ordinary skill in the art include (1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of active workers in the field." (Emphasis added).[7] Further, The "hypothetical 'person having ordinary skill in the art' to which the claimed subject matter pertains

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[1] *In re Kaslow*, 707 F.2d 1366, 1374, 212 USPQ 1089, 1096 (Fed. Cir. 1983)
[2] *see also Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1563, 19 USPQ2d at 1116 (Fed. Cir. 1991)
[3] *See, e.g., Vas-Cath*, 935 F.2d at 1563; 19 USPQ2d at 1116.
[4] *Union Oil v. Atlantic Richfield Co.*, 208 F.2d 989, 996 (Fed. Cir. 2000)
[5] *See also* MPEP §2163 II(A).
[6] 713 F.2d 693, 696, 218 USPQ 865, 868 (Fed. Cir. 1983), *cert. denied*, 464 U.S. 1043 (1984)

would, of necessity have the capability of understanding the scientific and engineering principles applicable to the pertinent art."[8]

The Disclosure Provides Sufficient Written Description for the Claimed Invention

Claim 25 recites a method for the treatment of a patient having need to inhibit TGFα-HII comprising: administering to the patient a therapeutically effective amount of an antibody that inhibits TGFα-HII and is capable of binding to a TGFα-HII polypeptide or fragment.

When the instant specification is read as a whole, it is clear that the inventors were in possession of the claimed method for treatment with antibodies capable of binding to a TGFα-HII polypeptide or fragment.

The Examiner states that no basis is seen for administering chimeric antibodies (claim 41) humanized antibodies (claim 42) single chain antibodies (claim 43) and FAB fragments (claim 44) in the specification.

Support for claims 41-44 can be found for example at page 26. More specifically support for chimeric antibodies can be found for example at page 26, para [0127], support for human antibodies can be found for example at page 26, para [0127], and page 26, para [0128] (administering to "preferably a nonhuman "animal is an implicit disclosure of administering also to humans); support for single chain antibodies can be found for example at page 26, para [0127]; and support for FAB fragments can be found, for example, at page 26, para [0127]. Withdrawal of this rejection is respectfully requested

The Examiner states that although original claim 19 does list ranges 1-374 and 46-374 as well as a polypeptide encoded by the cDNA contained in the ATCC deposit, no basis is seen for the other named ranges.

Applicant has indicated that the ranges in claim 25 were amended to reflect the correction in amino acid ranges as discussed for page 5 of the specification. Support for these corrections is provided in the specification for the reasons set forth above. Withdrawal of this rejection is respectfully requested

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[7] *See also* MPEP §2141.03.

[8] *Ex parte Hiyamizu*, 10 USPQ2d 1393, 1394 (Bd. Pat. App. & Inter. 1988) (emphasis added)

The Examiner states that a discussion as to what amino acids are identified as the leader sequence or transmembrane sequence cannot be construed as providing a basis for claiming antibodies that specifically bind to particular fragments.

In response the Examiner is directed to original claim 21 which claimed an antibody against the polypeptide of claim 19. As discussed above claim 19 provided the listed ranges as well as different sized fragments of the polypeptide. Clearly there was written support in the application for an antibody against the polypeptides set forth in original claim 19. Withdrawal of this rejection is respectfully requested

The Examiner indicates that the information concerning the deposit on page 6 of the specification does not make clear what cDNA sequence is actually contained in the ATCC deposit.

Applicant respectfully requests that the Examiner clarify this objection because the Applicant does not understand the Examiner's concern. Applicant did state in the prosecution of parent application 09/227,853 that DNA encoding the full-length sequence of SEQ ID NO:2 is present in the recited deposit.

The Examiner notes that the specification has been amended to change the date of deposit of ATCC 97160 from 15 May 1995 to 24 May 1995. The Examiner requests that Applicant supply copies of the same evidence presented in Parent application 09/227,853 to complete the instant specification.

In response Applicant encloses a copy of the ATCC Receipt which sets forth the date of May 24, 1995 for receipt of deposit 97160. Withdrawal of this rejection is respectfully requested.

4. Rejection under 35 U.S.C. 112, first paragraph, enablement

Claims 25 and 31-44 stand rejected under 35 U.S.C. 112, first paragraph, as allegedly failing to comply with the enablement requirement. The specification allegedly fails to identify those patients having need to inhibit TGFα-HII. It is allegedly not known what characteristics or medical conditions such patients must possess. Further the specification allegedly fails to identify any antibodies that bind to any portion of SEQ ID NO:2 that are capable of inhibiting TGFα-HII either in vitro or in vivo. Finally the Examiner states that the specification allegedly

fails to identify any fragments of SEQ ID NO:2 (including any 30 to 50 contiguous amino acid ranges) or any polypeptides at least 70% identical to SEQ ID NO:2 that could be used to generate antibodies that have the property of in vivo inhibition of TGFα-HII for any therapeutic purpose. For the following reasons Applicants disagree with this analysis.

The Legal Test for Enablement

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure provided by applicants coupled with information known in the art at the time the invention was made, without undue experimentation.[9] [10] Accordingly, the test for enablement is not whether any experimentation is necessary, but whether, if experimentation is required, it is undue.[11] The mere fact that an extended period of experimentation is necessary does not make such experimentation undue.[12] [13]

A finding of lack of enablement and a determination that undue experimentation is necessary requires an analysis of a variety of factors *(i.e.,* the *In re* Wands factors). The most important factors that must be considered in this case include: 1) the nature of the invention; 2) the level of one of ordinary skill in the art; 3) guidance provided in the specification; 4) the state of the prior art; and 8) the breadth of the claims.

"How a teaching is set forth, by specific example or broad terminology, is not important"[14] [15]. "Limitations and examples in the specification do not generally limit what is covered by the claims" MPEP § 2164.08. The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. It is well settled that patent applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art. The legal standard merely requires

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[9] MPEP §2164.0120

[10] *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998)) *United States v. Telectronics, Inc.* 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1998))

[11] *In re Angstadt*, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976)

[12] *In re Colianni*, 561 F.2d 220, 224, 195 USPQ 150, 153 (CCPA 1977)

[13] MPEP §2164.06.

[14] MPEP §2164.08

[15] *In re Marzocchi*, 439 F. 2d 220, 223-4, 169 USPQ 367, 370 (CCPA 1971)

that there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the invention as broadly as it is claimed.[16]

The Disclosure provides sufficient information to enable the claimed invention

Claims 25 and 31-44 are directed to a method for the treatment of a patient having need to inhibit TGFα-HII comprising administering to the patient a therapeutically effective amount of an antibody that inhibits TGFα-HII and is capable of binding to a TGFα-HII polypeptide.

Applicants have amended claim 25 to cancel the recitation of a polypeptide which is 70% identical to the TGFα-HII.

The Examiner states that it is not known what characteristics or medical conditions such patients must possess.

The specification clearly indicates that antibodies capable of binding to an TGFα-HII polypeptide would be useful for the treatment of a number of medical conditions. Page 18, paragraph [0093] states that potential antagonist compounds include an antibody ...which binds to the polypeptide. Page 19, paragraph [0096] states that antagonists may be employed to treat neoplasia, for example cancers and tumors. Page 19, paragraph [0097] states that antagonists to the polypeptides of the present invention may also be used therapeutically for the treatment of certain skin disorders, for example psoriasis. Page 24, paragraph [0119] states that antibodies specific to TGFα-HII may be used for cancer diagnosis and therapy, since many types of cancer cells up-regulate various members of the TGFα family during the process of neoplasia or hyperplasia. Withdrawal of this rejection is respectfully requested.

The Examiner states that the specification allegedly fails to identify any antibodies that bind to any portion of SEQ ID NO:2 that are capable of inhibiting TGFα-HII either in vivo or in vitro.

As discussed above, the specification provides, for example, on page 26, paragraphs [0127] – [0130] methods for the generation of antibodies capable of inhibiting TGFα-HII. The specification provides the complete amino acid sequence for TGFα-HII and the Examples

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[16] *Enzo Biochem., Inc. v. Calgene, Inc.*, 188 F.3d 13 62 (Fed. Circ. 1999), at 1372 (quoting *In re* Vaeck, 947 F.2d 488, 496 (Fed. Cir. 1991)).

provides methods of expressing and isolating the protein in E. coli (Example 1), baculovirous (Example 2) and COS cells (Example 3). One skilled in the art given the disclosure in the specification and the knowledge in the art could readily generate antibodies capable of inhibiting TGFα-HII. Withdrawal of this rejection is respectfully requested.

Finally the Examiner states that the specification allegedly fails to identify any fragment of SEQ ID NO:2 (including any 30 to 50 contiguous amino acid ranges) or any polypeptides at least 70% identical to SEQ ID NO:2 that could be used to generate antibodies that have the property of in vivo inhibition of TGFα-HII for any therapeutic purpose.

Applicants have amended claim 25 to cancel the recitation of least 70% identical to SEQ ID NO:2 rendering this part of the rejection moot. As discussed above the specification does provide support for any fragment of SEQ ID NO:2 (including any 30 to 50 contiguous amino acid ranges) that could be used to generate TGFα-HII antibodies. Page 26, paragraphs [0127]-[130] provide methods for generation of antibodies capable of inhibiting TGFα-HII from fragments. Withdrawal of this rejection is respectfully requested.

The Examiner states that the specification fails to provide that there is a correlation between any in vitro antibody binding and any in vivo inhibition of TGFα-HII for any therapeutic purpose. Applicants have amended claim 25 to recite that the antibody inhibits TGFα-HII. Accordingly Applicants are claiming antibodies which will function to inhibit TGFα-HII. As discussed above the specification provides support for the generation of such antibodies at page 26, paragraphs [0127] – [0130]. One skilled in the art given the specification could generate antibodies which inhibit TGFα-HII. Withdrawal of this rejection is respectfully requested.

Please direct any calls in connection with this application to the undersigned at the number provided below.

Please charge any additional fees, including additional fees for extension of time, or credit overpayment to Deposit Account No. 08-1641 (Attorney Docket No.: 39766-0151US D2).

Respectfully submitted,

Date: February 23, 2007

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